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Neuronal Polarity and the Epithelial Metaphor

Minireview Commentary

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How do neurons sort newly synthesized proteins and lipids and target these components to subdomains of the plasma membrane surface? Since neurons and glial cells arise from a thin epithelial sheet, it has seemed reasonable to anticipate that the general principles underlying epithelial cell polarity may be applicable to the neuron, and to a certain extent, this is turning out to be true. In fact, it has been suggested that basolateral and apical domains of epithelial cells correspond to the somatodendritic and axonal surfaces of neurons, respectively (Dotti and Simons, 1990). Many studies have attempted to directly test this hypothesis and the results, as summarized by Winckler and Mellman (1999 [this issue of *Neuron*]), have revealed that the neuronal surface is much more complicated than originally anticipated. Furthermore, despite initial expectations, it has been difficult to identify discrete "apical/axonal" sorting signals for neuronal proteins (Jareb and Banker, 1998).

Perhaps this should not come as such a surprise. In this essay, I contend that the basic morphological characteristics of an epithelium may be identified not only in the primitive neuroepithelium but also in the mature brain, even though the brain substance expands so greatly in the course of development that these persistent characteristics may not be immediately recognizable. The conclusion that one might have predicted from studies on embryos completed decades ago and in the absence of any contemporary polarity or trafficking information is that the neuronal surface in the CNS is, in its entirety, an equivalent of the lateral and basal domains of an epithelium. This implies that there may no longer be representation of the apical domain on the neuronal surface at all, but that instead, the neuron has over the course of evolution developed some highly unique subpartitioning mechanisms of the basolateral domain that we just do not understand yet. Recent studies on the targeting of neurotransmitter receptors to the neuronal surface (Rubio and Wenthold, 1997; Stowell and Craig, 1999) and the existence of as yet poorly understood neuronal surface membrane diffusion barriers (Winckler et al., 1999) may be adduced in support of this point of view. This argument should not be dismissed as merely a semantic one; the metaphor of the axon as an "apical" derivative frequently finds expression in the literature; acceptance of this notion limits our comprehension of the full scope of the polarity principles operative in the neuron.

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General Features of an Epithelium

Epithelial cells line the body surface and body cavities. Within the organism, continuous epithelial sheets wall off fluid-filled lumena from the extracellular milieu of the underlying tissue. An epithelium may be one or many cells thick before sitting down on a basal lamina, the complex elaboration of extracellular matrix molecules that forms the definitive border of the epithelium with nonepithelial cells. The presence therefore of an "interior" lumen (whose boundary is the apical domain) and an "external" basal lamina (the basal domain) therefore defines the extent of the epithelium. In between these two domains is found the lateral domain.

Luminal content and the extracellular milieu are generally dissimilar in composition; this is maintained in large measure by the epithelial cell structure and physiology. The organization of the plasma membrane is critical for the proper function of the epithelium (Figure 1). The luminal (apical) and parenchymal (basal and lateral; but usually written as "basolateral") domains along the plasma membrane are structurally defined by the presence of tight junctions that form a morphological network and a physiological fence that sharply segregates apical and basolateral domains. Tight junctions are critical elements, particularly in transporting epithelia (Le Gall et al., 1995), but in certain epithelia, tight junctions are absent. Subjacent to the tight junctions, adherens junctions and desmosomes join the lateral surfaces of epithelial cells to one another. These adhesive devices, linked to intracellular cytoskeletal elements, physically strengthen the epithelium, an important property in those epithelia that are subject to mechanical stress or pressure differentials, as in the intestines or bladder. In addition, the adherens junction may mediate signal transduction as well (Gumbiner, 1996). In all epithelia, the plasma membranes of participant cells are in very close proximity to one another—100–300 Å at most—so there is very little extracellular space.

Phylogenetically and Developmentally, the Brain Is an Epithelium

In Chordata, the nervous system begins as a superficial, simple epithelial sheet that in general displays the foregoing features (Figure 2). After invagination and neural tube closure, the topological relationships between constituent cells and their surroundings are maintained, and so a luminal and a lateral intercellular compartment is evident, and the tube is separated from nonneural elements by the basal lamina. As the cells of the neural tube divide, seek new positions, and interconnect and the brain mass expands, the central lumen is maintained as convoluted ventricles and connecting passages—distorted from their original shape but nonetheless a lumen. The ventricular lumen is lined by a simple epithelial layer of ependymal cells with apical microvilli. These cells interconnect via a complex set of junctions on their lateral surfaces. No matter how massive the brain substance proper becomes, as measured by the distance from the apical ependymal lining to the brain surface at a given point, the brain still retains its epithelial

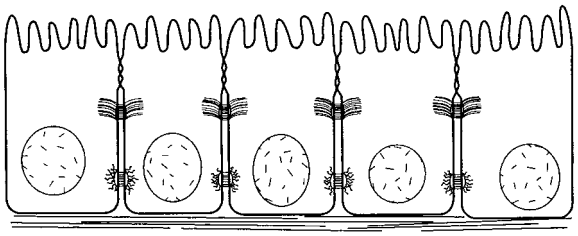

Figure 1. The Basic Organization of an Epithelial Cell Layer

In a simple epithelium, cells are linked together via stereotypically arranged junctions at the lateral cell borders. Tight junctions separate an apical from the lateral plasma membrane domain. Adherens junctions and desmosomes link lateral cell surfaces. The epithelial sheet lies on a basal lamina that is composed of extracellular matrix molecules.

character and so is bounded by the basal lamina at the pial surface (Figure 3).

This analysis puts the neuron—the entire neuron and all its processes—abutting what in a simple epithelial cell is termed the basolateral domain. Let's consider the implications of this statement. If it were true, then we would expect that as a neuron makes contact with another neuron, a "lateral" domain junctional specialization should be found. This is the certainly the case (see below). When a neuron contacts a nonepithelial cell, however, a basal lamina, and not a lumen or a lateral specialization, should be interposed. And this is so. Wherever a neuroepithelial-derived cell makes contact with a nonepithelial derivative, there is a recognizable basal lamina. It is the case within the brain parenchyma, into which blood vessels penetrate but are separated from the neural elements by a basal lamina, and in the periphery, where the basal lamina invests the neural

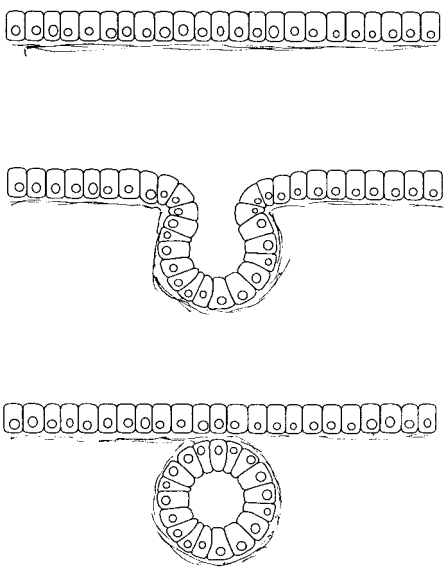

Figure 2. Borders of the Neuroepithelium

The nervous system begins as a simple epithelial sheet that, following invagination and neural tube closure, creates an apical enclosed lumen. The neural tube is separated from surrounding nonepithelial tissues by a basal lamina.

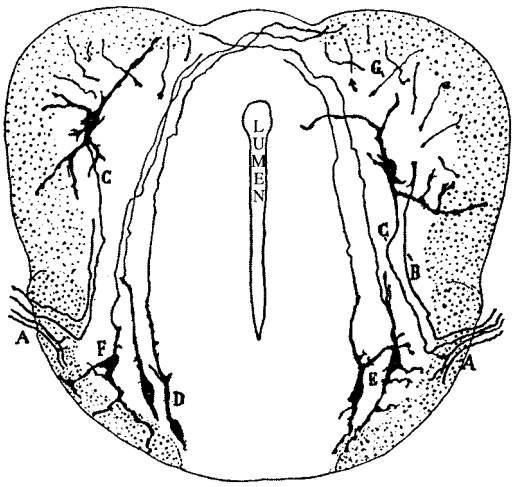

Figure 3. Neurons Do Not Have Contact with a Lumen

In this drawing of a 20 day human spinal cord from Ramón y Cajal (1995), the expansion of the brain parenchyma during neurogenesis yields cell bodies and their processes completely contained within the tissue space between the apical lumen and basal pial surface. This puts all neural elements in a domain in the nervous system "equivalent" to the basolateral domain of an epithelium.

crest–derived Schwann cells that ensheath axons. A basal lamina is also interposed between the synaptic terminations of the axons and their effector organs (e.g., at the neuromuscular junction).

Neuronal Surfaces Abut the "Lateral" Domains of Other Neurons

The concept that the neuron lies wholly within the basolateral compartment (Figure 4) may also be deduced from an analysis of the plasma membrane specializations that are assembled on its surface. The neuron does not make tight junctions, consistent with the argument that it cannot segregate off an apical domain for itself; neither does the neuron make desmosomes (Peters et al., 1991), possibly because it is not subject to mechanical stresses. However, adherens junctions abound on the neuronal surface; these junctions connect it to other neurons, and it is at these adherens junctions that the physiological synapse is found. The argument has been presented that the adherens junction is the evolutionary antecedent of the chemical synapse (Fannon and Colman, 1996; Shapiro and Colman, 1999). In brief, the evidence for this is that the epithelial adherens junction and the CNS synaptic junctional complex are morphologically similar adhesive and signaling devices consisting of plasma membrane thickenings with underlying electron-dense material. There is a narrow, remarkably uniform cleft between plasma membranes of ~150–300 Å. The junctional membranes are invariantly in register, parallel to one another, and cannot be separated from one another by physical means. Most telling, it has recently become clear that the adherens junction and the CNS synapse share identical adhesive elements, in that both are at least in part cadherin mediated structures, containing not only these calcium-dependent adhesion molecules but cadherin-associated proteins as well (Uchida et al., 1996).

One might argue that there are problems inherent in

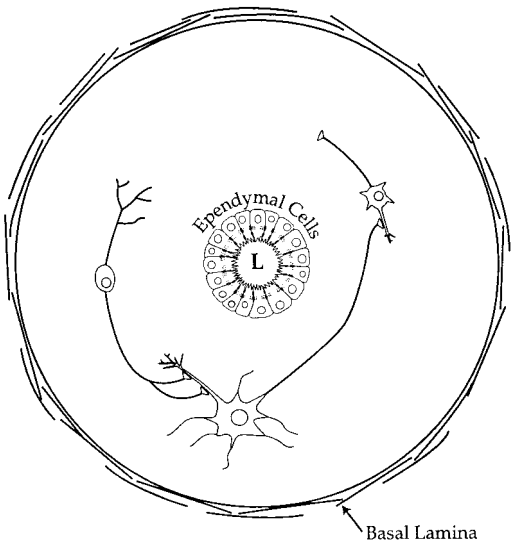

Figure 4. The Synaptic Junctional Complex in the CNS, an Adherens Junction Derivative, Is Found All Over the Neuronal Surface

Conceptually, neurons in situ abut the basolateral domain of an epithelium and therefore express only the features of that domain on their surface. The synaptic junctional complex in the CNS is essentially an epithelial adherens junction, a specialization of the lateral domain that is further specialized by neurons for highly sophisticated cell–cell communication.

the foregoing analysis. In particular, in epithelia, adherens junctions connect each cell in its layer to its immediately adjacent, laterally positioned neighbors, and not to distant cells in "other" layers. This "somacentric" view of simple epithelial attachments must however be broadened when considering CNS architecture. In the CNS, axons and dendrites interconnect in a staggeringly complex three-dimensional neuropil; where are the laterally connected cellular layers? Although cell body layers are of course apparent in the mature CNS—in cortical structure, for example—more importantly, dendritic and axonal plasma membrane domains are frequently organized in clearly recognizable layers or lamina (as in retina, optic tectum, and hippocampus). In the CNS, physiologically coupled neurons are physically interconnected via adherens (synaptic) junctions placed along axons and dendrites that have evolved to operate at substantial distances from the cell body. Thus, in the CNS epithelium, physical connection and consequent neuronal activity may be thought of as "action at a distance." But essentially the same adherens junction that links adjacent simple epithelial cells also links neurons via their axonal and dendritic extensions.

In summary, by relegating the apical domain in the brain to its proper and only surface—the ependymal lining facing the ventricular lumen—and thereby completely dissociating it from axonal polarity, we are conceptually positioned to reframe the question of how neurons sort and target proteins. In essence, we free up the axon from the constraints of an "apical" designation and consider it purely as a greatly elongated Golgi apparatus-to-plasma membrane compartment (the absence of ribosomal subunits in axons in Chordata is one strong argument for this last contention). We should develop, I think, a different framework upon which to evaluate the full complement of mechanisms that act to polarize so many types of neuronal cell surfaces in three-dimensional space.

Some of the fundamental subcellular mechanisms that organize the plasma membranes of uniform, simple epithelia are of course utilized also by neurons. However, these mechanisms—and the experiments reviewed by Winckler and Mellman (1999) clearly reveal this—are insufficient to account for the complex polarity observed in the numerous neural cell phenotypes. Neurons have greatly expanded upon the basic mechanism repertoire and have evolved novel and highly sophisticated strategies to differentially distribute, with exquisite and absolute precision, the intracellular protein traffic, such that within even "simple" dendritic and axonal arborizations, multiple plasma membrane subdomains may be discerned (Craven et al., 1999; Serafini, 1999; Winckler et al., 1999).

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